Treatment of Disease: The role of Knowledge Representation for Treatment Selection

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1 Treatment selection

Treatment is the care and management of a patient to combat, ameliorate, or prevent a disease, disorder, or injury.[1] It may be *active* if directed to the cure of the disease, *causal* if directed against the cause of the disease, *palliative* if only aims to relieve pain or distress with no attempt to cure, *preventive* if aims to prevent the occurrence of a disease, etc. The goal of treatment selection is to help practicing clinicians gain and apply the knowledge and standards in order to select the best possible treatment for a patient [3]. Managing a patient's care involves alternating between diagnosis (assessment) and treatment over a period of time [13]. The treatment portion involves a series of decisions, where each one requires selecting among several alternative courses of action [7].

Research on medical judgment has raised deep questions about how clinicians make decisions and plan treatment, particularly when they are faced with uncertainty and information overload. This has lead to the proposal of artificial intelligence methods that support decision making for treatment selection [7]. Knowledge about the effectiveness of treatments must be based on empirical evidence which is, for the most part, produced by scientific research and published in scientific literature. However, extracting this knowledge from research outcomes is not trivial. Indeed, even for someone who is deeply imbued in statistical procedures and nuances, it is very difficult to know what research findings really mean at the level of clinical practice [4]. One of the most significant obstacles in the practice of personalized medicine is the translation of scientific discoveries into better therapeutic outcomes [29].

For most diseases, selecting a treatment is complex because every patient is unique, and many symptoms and diagnoses are imprecise in their definition [30]. For instance, in the case of infectious diseases, the complexity of the problem is so large that it is highly unlikely that clinicians will be capable of delivering optimal treatment to all patients [16]. Therefore, some clinicians believe that providing

[1] Mosby's Medical Dictionary, 8th edition in theFreeDictionary.com

decision support tools may improve the quality of care a patient receives through providing better treatment choices [24].

Helping the clinician select a certain treatment is a multi-objective decision problem that must address different questions [6], such as:

- What would be the most cost-effective treatment?
- How may we plan a treatment regime to cover for possible contingencies?

Knowledge-based systems (KBS) can help practitioners by evaluating the potential outcomes for multiple courses of action. For instance, decision-theoretic KBS can compare alternative treatment policies by combining measures of outcome likelihood with estimates of utility [6].

The next section provides an overview of the main knowledge representation techniques that can be applied for treatment selection. This is followed by a section that presents some representative examples of applications of these techniques. The section concludes by introducing the two systems that will described in the following two chapters. The first proposes combining a logical and probabilistic approach for predicting adverse drug reactions from electronic medical records. The second considers a decision-theoretic model for patient-tailored virtual rehabilitation.

2 Knowledge representation techniques

The following list presents some of the main KR techniques appropriate for treatment selection. The list is not intended to be exhaustive but only to give a broad overview of the possibilities.

- **Rule-based systems**: Rule-based systems are perhaps one the most simple, yet powerful KR methods. Knowledge is encoded in the form of IF-THEN-ELSE rules, and the set of all rules form the *rule base* or *knowledge base*. Finally, the *inference engine* answers questions given to the system by applying the rules to the given data or *working memory*. An example is Lee et al.'s [14] system for monitoring diabetes that combines rule-based knowledge with a k-nearest neighbour classifier to recommend a treatment.
- **Logic of argumentation**: The logic of argumentation is a variant of standard first-order logic where an argument has the form of a proof but does not prove its conclusion [7]. In contrast to classical logic, in argumentation p and $\neg p$ can both be inferred from the same knowledge database. This can occur because the KB is split into subsets, called *theories*, that are internally but not necessarily mutually consistent. The decision making process in argumentation ranks possible solutions in terms of the supporting arguments formed by claims, grounds and confidence. Toxicology and risk assessment in genetics are among the examples where argumentation has been useful [7].
- **Fuzzy set theory and fuzzy logic**: The adjective fuzzy encompasses the notion of a degree of membership. In this sense, a fuzzy set is a set where

a bounded function of membership is defined over its members. Translated to logic, this means that inferences are not restricted to being either true or false, but that they can capture different shades of belief. A number of treatment selection systems use fuzzy set theory and fuzzy logic including the fuzzy-ARDS for the intensive care data of patients with acute respiratory distress syndrome (ARDS) [1] and Ying et al.'s [30] system for determining optimal HIV/AIDS treatment regimens.

– **Bayesian decision-theoretic systems**: In general, Bayesian models are based on probabilities which are updated as new evidence becomes available. Bayes' theorem, which is central to these systems, facilitates inference from existing knowledge. Probabilistic graphical models, which combine an intuitive visual representation with rigourousness of statistics, express (statistical) conditional independencies, which are often admitted as proxies for causality. Perhaps the best known Bayesian decision-theoretic framework is Bayesian networks whose viability for treatment selection is illustrated by a simple pathophysiological model of infection to choose antibiotic treatment [2]. Of course, more advanced models, such as influence diagrams, Markov decision processes (MDPs), and partially observable MDPs (POMDPs) among others, are also appropriate for treatment selection.

In general, knowledge representation framework optimized for one task, such as diagnosis, might perform only poorly in another task, such as treatment selection [20]. Recently, **machine learning** techniques have been incorporated to the library of plausible tools to build or improve recommendation systems based on different representation techniques. This is illustrated in the two examples that are described at the end of this chapter. One uses data from medical records to build a rule-based system for predicting adverse drug reactions. The other uses reinforcement learning to improve a model for adapting a virtual rehabilitation environment to the patient progress.

3 Medical applications

Existing expert and decision support systems tend to focus on diagnosis, and only a few systems deal with treatment selection [23]. Nevertheless, decision-support systems for treatment selection have made an impact in several different medical domains. This section provides some representative examples of treatment selection for a couple of domains.

Treatment selection for infectious diseases is an area that has received attention since the early days of artificial intelligence. The MYCIN system was one of the first rule-based expert systems to attempt to determine anti-infective treatment for septicaemia and meningitis (Shortliffe 1976 in [6]. Since then a number of decision support models focused on treatment selection for infectious diseases have been developed based on different computational techniques including logistic regression, Bayesian approaches, and neural networks [24, 2]. Nosocomial infections are sub-domain of infectious disease that have received particular attention [16, 24], and a canonical system for this task is the Health Evaluation by Logical Processing (HELP) system [17].

The worldwide prevalence of diabetes is overwhelming as currently about 2.2% of the world population suffers from it. This percentage is estimated to rise to 4.4% by 2030, which translates to more than 300 million people [28]. Therefore, it is unsurprising that a number of decision-support systems for treatment selection in diabetes have been developed. Some are integrated into the hospital environment, like the DIACONS system [23], while others are developed for ubiquitous healthcare [14].

An exhaustive list of domains is beyond the scope of this section, but it is easy to find examples of knowledge representation based treatment selection systems in HIV/AIDS [30], breast cancer [13], anemia [22], dyspnoea and bronchospasm [6], glaucoma e.g. CASNET [27], acute respiratory distress syndrome (ARDS) [1], rehabilitation [10] and psychotherapy [3] among others.

Some decision-support systems do not focus on specific diseases but instead intend to be a more comprehensive tool. One example that supports treatment selection is the Oxford System of Medicine [8, **?**], which is a project aimed at developing a comprehensive information management and decision support system for general practitioners (GPs).

Next, we briefly introduce the two treatment selection systems presented in the following chapters.

4 Personalized medicine: predicting adverse drug reactions

One issue that a doctor faces when treating a patient is selecting a medication to prescribe. This task has received increased attention because there have been several dramatic examples of patient variation in response to drugs such as Rofecoxib (Vioxx$^{\text{TM}}$) and Coumadin$^{\text{TM}}$ [18, 11]. These extreme variations in response are known as Adverse Drug Reactions (ADRs) [12, 9, 19], and they are the fourth-leading cause of death in the United States and represent a major risk to health, quality-of-life and the economy [21]. For example, the pain reliever Vioxx$^{\text{TM}}$alone was earning US$2.5 billion per year before it was found to significantly raise the risk of heart attack and was pulled from the market while other similar drugs remain on the market [18, 11].

These cases have highlighted the need for tools that can help a doctor more accurately determine which drug and dosage to prescribe to a patient. This may be possible now due to the shift in healthcare practice towards the wide spread use of electronic medical records (EMRs), which are databases that store a patient's clinical history. Thus, the relevant data reside on disk as opposed to paper charts. Therefore, machine learning and data mining techniques could be applied to EMR data in order to build decision-support models to help doctors decide which medication to perscribe to which patient.

When EMRs are based on relational databases (a common choice), their relational schemas (i.e., the database contains separate relational tables for diagnoses, prescriptions, labs, etc.) pose challenges from a knowledge representation perspective. When analyzing such data it is important to capture important relationships (e.g., time of diagnosis may be relevant) as well as to model the uncertain, non-deterministic relationships between patients' clinical histories and current and future predictions about their health status. Yet traditional learning and mining paradigms have almost exclusively focused on handling propositional data. That is, data residing in a single table, where each row represents a data point and the rows in the table are assumed to be independent. It is non-trivial to convert an EMR into a single-table because different patients may have dramatically different numbers of entries in any given table, such as diagnoses or vitals. Chapter **XX** will discuss three different strategies that address this problem such that statistical models can be learned from relational EMR data. We will present an evaluation of the different methodologies on three real-world ADR tasks.

5 Patient-tailored rehabilitation: automatic adaptation to the patient

The consequences of strokes worldwide are devastating. They are the first-leading cause of disability, the second-leading cause of dementia, and the third-leading cause of death (more than five million deaths a year). Furthermore, they are a major cause of epilepsy, falls and depression and their prevalence exceeds 30 million people worldwide [5]. In the US alone, the estimated cost of strokes in 2007 surpassed $40 billion USD. Long-term care for stroke rehabilitation will benefit from strengthening health systems, and developing innovative therapies. A rising star among these new generation of therapies is *virtual rehabilitation* [15], which is a therapy paradigm that exploits the power of computers to provide a training environment with unmatched capabilities for tailoring the treatment to a specific patient.

Since the mid nineties, a number of virtual rehabilitation platforms have been developed with different salient features [26]. Gesture Therapy (GT) [25] is an upper limb virtual reality-based motor rehabilitation platform whose major strength is the extensive use of advanced decision theoretic models in order to support adaptation of the therapy to the changing needs of the patient. GT is an example of intelligent rehabilitation, a modality which exploits knowledge representation and reasoning to create assistive technology capable of generating actions, that is, decisions, emulating those of an expert.

Chapter **XX** of this book details the probabilistic decision model underlying the critical feature of GT: adaptation. Adaptation is the pillar of intelligent rehabilitation because it is the central feature that allows an otherwise static virtual environment to change its behaviour to fit a patient's overall progress in a manner that imitates the decisions a therapist would make as he observes the advance of the patient.

The decision model of GT is designed to optimise the task challenge expressed by the virtual environment with regards to patient exhibited performance. The knowledge representation formalism is a Markov decision process (MDP) enriched with a reinforcement learning strategy that upgrades the static MDP to a dynamic decision model that keeps the decision policy, i.e., the reasoning, updated throughout the therapy.

Chapter **XX** opens with a discussion on the need and importance of adaptation. Then, it proceeds to overview possible alternatives for implementing this feature that capitalise on knowledge representation. Finally, it presents an experimental evaluation of the adaptation model of the GT platform evidencing the general trend of the model decisions to learn and mimic the human therapist decisions.

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